REMARKS

I. STATUS OF THE APPLICATION AND CLAIMS

Claims 4-8, 10, and 11 are currently pending for examination, with amendments to claims 4 and 5 as set forth above.

Specifically, claims 4 and 5 have been amended to delete reference to polypeptides "comprising a deletion, substitution, or addition of one or more amino acid of the monoclonal antibody region" and to polynucleotides comprising "deletion, substitution, or addition of one or more nucleotides in the nucleotide sequence shown in SEQ ID NO: 1." Support for these amendments to claims 4 and 5 can be found in original claims 4 and 5 and throughout the specification.

Claims 4 and 5 have also been amended to recite a polypeptide that does not contain "an N-terminal region of the Reelin protein that has homology to F-spondin" or a nucleotide sequence not "encoding an N-terminal region of the Reelin protein that has homology to F-spondin," respectively. Support for these amendments can be found in original claims 4 and 5 and throughout the specification, at least at page 5, lines 1-2.

Thus, the claims are fully supported by the application as originally filed and the amendments add no new matter.

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. New Matter Rejection

The Examiner rejects claims 4-8 and 10-11 under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. Action, at pages 2-3. Specifically, the Examiner states that:

> the specification does not support the newly generic recitation of polypeptide defined by recognition by a monoclonal antibody that binds

> SEQ ID NO: 2. The previous language and language supported by the specification denot [sic] a particular CR-50 antibody of the prior art, yet the new recitation is deemed to improperly broaden, as the peptide encompassed may be any that is noted to be capable of binding a [sic] antibody that binds SEQ ID NO: 2. The species of CR-50 does not support the newly recited genus of peptides so encompassed. Moreover, while the specification provides for the recitation of neither a repeat site nor a F-spondin domain, the exclusion does not appear to be supported as to the new exclusion of peptides not comprising any portion of an F-spondin domain. . . . Thus, the noted recitations constitute new matter.

Action at page 3. Applicants respectfully traverse this rejection.

The language "a region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2" is fully supported by the specification. SEQ ID NO: 2 is a portion of the Reelin protein corresponding to amino acids 230-346. Specification at page 4, lines 11-12, and at page 11, lines 23-24. Amino acids 230-346 of the Reelin protein correspond to the CR-50 epitope region. *Id.* A monoclonal antibody that binds to SEQ ID NO: 2 is therefore a monoclonal antibody that binds to a portion of the Reelin protein corresponding to amino acids 230-346. The specification clearly supports the recitation of such an antibody: SEQ ID NO: 2 was identified as the CR-50 antibody epitope region because it immunoprecipitated with that antibody. *Id.* at page 11, lines 19-21. A "region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2" is thus SEQ ID NO: 2 or a polypeptide sufficiently similar to SEQ ID NO: 2 that the polypeptide is recognized by a monoclonal antibody that binds to SEQ ID NO: 2. SEQ ID NO: 2 is disclosed by the application, as is the CR-50 antibody that binds to SEQ ID NO: 2. Thus, the language "region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2" is not new matter.

The Examiner also alleges that the recitation of the language "any portion of an F-spondin domain" is new matter. Claims 4 and 5 have been amended, and no longer contain that language. Thus the rejection with respect to that language is moot.

Applicants therefore maintain that amended claims 4 and 5 and claims 6-8 and 10-11, which depend therefrom, do not contain new matter. They respectfully request reconsideration and withdrawal of the rejection.

B. Written Description Rejection

The Examiner maintains the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Action at page 4. The Examiner states:

> [a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence encoding the polypeptide sequence SEQ ID NO: 2 and no other nucleic acid or amino acid sequences that are proposed to correspond to the same structural and/or functional characteristics. While the specification does note certain functional recitations, for example the ability to bind, the specification fails to delineate by structure those molecules that exhibit the noted function. However, the ability to bind is an unpredictable characteristic as previously noted in Skolnick and Jobling of record. Given the fact that the specification fails to provide objective evidence of any additional sequences that are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim.

Action at page 6-7. Applicants respectfully traverse this rejection.

According to the Examiner, adequate written description support for the claimed polynucleotide genus would include "recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, **or** of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus." *Id.* at page 6 (emphasis added).

Claims 4 and 5, as amended, define the genus by suitable structural and functional features. In claim 4, the encoded polypeptide comprises either (a) a polypeptide sequence derived from a mouse Reelin polypeptide, (b) a polypeptide sequence corresponding to SEQ ID NO: 2, or (c) a polypeptide sequence encoded by a degenerate version of a nucleic acid sequence encoding (a) or (b). In all cases, the encoded polypeptide binds to the CR-50 monoclonal antibody and does not contain a repeat site or an N-terminal region of the Reelin protein that has homology to F-spondin. Similarly, claim 5 is limited to: (a) a polynucleotide comprising SEQ ID NO: 1, (b) a polynucleotide encoding a polypeptide capable of binding to a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2, or (c) degenerate versions of (a) and (b). In all cases, the polynucleotide encodes a polypeptide that contains neither a repeat site nor an N-terminal region of the Reelin protein that has homology to F-spondin.

Sequences falling within the scope of claims 4 and 5 are limited by both the short length of the unique segment of Reelin in which the epitope is found, amino acids 191-500 (see Fig. 4 of Tissir et al., Nat. Rev. Neurosci., 4:496-505, 2003, submitted with the Amendment dated March 1, 2004), and the ability to bind to the monoclonal antibody. The genus is thus structurally well defined. "[I]t may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other

appropriate language.'" *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

The Examiner further argues that "the antibody is only defined by its ability to bind a peptide having SEQ ID NO: 2, a circular definition which does not direct to those elements or sequences that may be included or varied such that binding still occurs to any portion thereof." Action at page 5. Applicants note that claims 4 and 5, as amended, do not include deletion, substitution, or addition variants of the claimed polynucleotides. Thus, that portion of the Examiner's reasoning is moot.

Applicants therefore maintain that the specification provides an adequate written description to support the scope of amended claims 4 and 5 and claims 8-11, which depend therefrom. They respectfully request reconsideration and withdrawal of the rejection.

C. Enablement

The Examiner also maintains the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 112, first paragraph, alleging that "the specification, while being enabling for the polynucleotide of SEQ ID NO:1, does not reasonably provide enablement for" certain recitations in claims 4-8, 10, and 11, and "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Action at page 7. Specifically, the Examiner alleges that:

> the claims are directed to polynucleotides encoding peptides with greater than single amino acid substitutions, deletions and insertions and to partial peptide fragments which bind an antibody that binds SEQ ID NO:2. Yet the specification fails to teach alternative sequences other than SEQ ID NO:2 encoded by SEQ ID NO:1 and degenerate sequences thereof, capable of binding such antibody that corresponds to the claim recitations.

> There is no disclosure of those residues which may be replaced, modified, inserted or deleted without abrogating the disclosed immunological reactivity. The functional recitation of binding is delimited only via that function, yet the specification does not teach the structural modifications encompassed while retaining function and the claim are therefore essentially unlimited in structure.

Id. at page 9. Accordingly, the Examiner alleges that one skilled in the art could not "practice the invention as broadly claimed without undue experimentation." *Id.* at page 7. Applicants respectfully traverse the rejection.

Claims 4 and 5, as amended, do not contain reference to deletion, substitution, or addition of one or more amino acids of the monoclonal antibody recognition region. Thus, the portion of the Examiner's rejection pertaining to variants of the claimed sequences is moot.

As discussed above, in claim 4 the encoded polypeptide comprises either (a) a polypeptide sequence derived from a mouse Reelin polypeptide, (b) a polypeptide sequence corresponding to SEQ ID NO: 2, or (c) a polypeptide sequence encoded by a degenerate version of a nucleic acid sequence encoding (a) or (b). In all cases, the encoded polypeptide binds to the CR-50 monoclonal antibody and does not contain a repeat site or an N-terminal region of the Reelin protein that has homology to F-spondin. Similarly, claim 5 is limited to: (a) a polynucleotide comprising SEQ ID NO: 1, (b) a polynucleotide encoding a polypeptide capable of binding to a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2, or (c) degenerate versions of (a) and (b).

The Examiner admits that the specification teaches "SEQ ID NO: 2 encoded by SEQ ID NO: 1 and degenerate sequences thereof . . . ." Action at page 9. SEQ ID NO: 1 contains 351 nucleotides, and SEQ ID NO: 2 contains 117 amino acids. The section of Reelin containing the monoclonal antibody epitope and not including either a repeat

region or an N-terminal region of the Reelin protein that has homology to F-spondin contains 310 amino acids. Moreover, the claims are further limited to polypeptides that are recognized by a monoclonal antibody that binds to SEQ ID NO: 2. CR-50 is such an antibody, and is described in the specification at least at page 3, lines 14-17. A "region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2" or "a polypeptide that binds to a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2" is SEQ ID NO: 2 itself or a polypeptide sufficiently similar to SEQ ID NO: 2 that the polypeptide is recognized by a monoclonal antibody that binds to SEQ ID NO: 2. Thus, the sequences potentially included within the claimed genus are clearly defined: they either comprise SEQ ID NO: 1 or comprise a sequence encoding SEQ ID NO: 2, or they are derived from the amino acid or nucleotide sequence of Reelin, which is known in the art. Furthermore, each sequence must (1) be recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2, and (2) lack a repeat region or an N-terminal region of the Reelin protein that has homology to F-spondin.

It would be a matter of routine experimentation, and not undue experimentation, for one of ordinary skill in the art to obtain polypeptides that bind to the antibody while lacking a repeat site or an N-terminal region of the Reelin protein that has homology to F-spondin. Sequence cloning, isolation, and production techniques are conventional. Screening tests for antibody binding are well known and have repeatedly been held by courts to be routine. Furthermore, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (internal citation omitted). In fact, the Office's own 1999 Interim Written Description Guidelines state, in Example 16, that "the level of skill and knowledge in the art of antibodies . . . was such that production of antibodies against a well-characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced." Likewise, production of and screening tests for antigens that bind to a known antibody are conventional. Additionally, the specification teaches, at least in Examples 2 and 3, how to detect, express, and purify polypeptides that bind to the monoclonal antibody.

Applicants therefore maintain that the specification fully enables amended claims 4 and 5 and their dependent claims 8-11. Reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph, enablement rejections is respectfully requested.

III. REJECTION UNDER 35 U.S.C. § 102

The Examiner maintains the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 102(b) as allegedly being anticipated by de Bergeyck et al., J. Neurosci. Methods 82:17-24, 1998 ("de Bergeyck"). Action at page 12. de Bergeyck discloses "[p]rotein H (for 'hinge')[, which] corresponds to residues 164-496 of the reelin sequence." de Bergeyck at page 22. The Examiner states:

> [w]hile it is agreed that the H164-496 peptide only comprises a portion (27 amino acids) of the F-spondin domain, such does not correspond to having an F-spondin domain. Moreover, the claims are directed to deletion, substitution and addition mutants. At the very least the H164-496 mutant may correspond to such recitations. The peptide does not comprise a F-spondin domain because the domain is not included in full and the mutant may further correspond to a mutant lacking any of an F-spondin domain while containing a 27 amino acid addition. While the new

> limitations of claims 4-5 denote that no portion may be of the F-spondin domain, the claim allows for structural variability inclusive of additions or [sic] one or more amino acids of the monoclonal antibody recognition region and degenerative sequences.

Action at pages 13-14. Applicants respectfully traverse.

Claims 4 and 5, as amended, specify that the polypeptide does not contain an N-terminal region of the Reelin protein that has homology to F-spondin. That language is commensurate with the definition of "F-spondin domain" provided by Applicants in the specification: "an N-terminal region of the Reelin protein that has homology to F-spondin." Specification at page 5, lines 1-2. As the Examiner admits, the H164-496 peptide comprises 27 amino acids of the F-spondin domain. Action at pages 13-14. That 27-amino-acid stretch of H164-496 is an N-terminal region of the Reelin protein, within the region of Reelin that has homology to F-spondin. Hence, de Bergeyck does not disclose all of the limitations of claims 4 and 5 and cannot anticipate the claims.

Furthermore, claims 4 and 5, as amended, no longer encompass variants of the claimed polypeptide and nucleotide sequences. Thus, the Examiner's contention that "the claim allows for structural variability inclusive of additions or [sic] one or more amino acids of the monoclonal antibody region" is moot. Furthermore, although the "comprising" language of claims 4 and 5 encompasses polypeptides containing additional amino acids to those in the monoclonal antibody binding region, those claims specifically state that such polypeptides cannot contain an N-terminal region of the Reelin protein that has homology to F-spondin. That is, polypeptides within the claim scope do not contain an amino acid sequence recognizable as a portion of the Reelin protein region that has homology to F-spondin. The H peptide contains a 27-amino acid sequence that corresponds directly to a 27-amino acid sequence of the F-spondin

domain. In the Examiner's example, "a mutant lacking any of an F-spondin domain while containing a 27 amino acid addition" that makes up a partial sequence of the F-spondin domain could not be considered to lack an N-terminal region of the Reelin protein that has homology to F-spondin. Action at page 14. The Examiner has previously admitted as much, stating that "de Bergeyck et al. does not teach a specific peptide immunogen consisting of the CR-50 epitope region and thus containing none of the F-spondin domain." Office Action mailed July 13, 2004, at page 16.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

IV. REJECTION UNDER 35 U.S.C. § 103

The Examiner maintains the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 103 as allegedly being unpatentable over de Bergeyck; Nakajima et al., PNAS 94:8196-8201, 1997 ("Nakajima"); and Miyata et al., J. Neurosci. 17:3599-3609, 1997 ("Miyata"). Action at page 15. The Examiner states that:

> one of skill in the art would be motivated to produce a pepetide [sic, peptide] consisting of the CR-50 epitope peptide to make CR-50 epitope specific antibodies capable of blocking the noted reeler phenotype as suggested by Nakajima and Miyata. One of skill in the art would expect success using such techniques given the high skill in the art of making antibodies specific to various peptide regions and the teachings of Miyata and Nakajima that it is the CR-50 epitope that directs the reeler phenotype. The antibody so generated would provide for the advantages of CR-50 in functional testing within the in vitro and in vivo model systems while containing neither a F-spondin domain nor repeat site. Thus, the cumulative reference teaching [sic] render the claimed invention obvious to one of skill in the art.

Id. at 16. Thus, the Examiner asserts that the reference teachings suggest producing a CR-50 epitope peptide in order to make an antibody that binds to the CR-50 epitope of

Reelin protein, which is capable of blocking the Reeler phenotype. Applicants respectfully traverse this rejection.

In repeating the rejection, the Examiner did not address Applicants' arguments, presented in their Amendment dated November 10, 2004, that the claimed invention is not obvious in view of de Bergeyck, Nakajima, and Miyata, either alone or in combination.

de Bergeyck is directed to identifying antibodies to Reelin protein that are different from the CR-50 antibody. After discussing the CR-50 antibody and its epitope, de Bergeyck states: "As reelin is such a large molecule, the understanding of its function would presumably benefit from the availability of additional antibodies directed against different portions of the molecule." de Bergeyck at pages 17-18. To obtain these antibodies, de Bergeyck creates peptides and "fusion proteins used for immunization or epitope localization." *Id.* at page 18, Fig. 1. The only uses disclosed for the peptides are to generate additional antibodies and to locate epitopes on Reelin that bind to those antibodies. Because de Bergeyck is concerned with identifying antibodies other than CR-50, peptides lacking the F-spondin domain or repeat sites are not employed.

Miyata does not cure the defect of de Bergeyck. Miyata discloses the inhibitory effect of the CR-50 monoclonal antibody on the regulation of Purkinje cell alignment by Reelin. Miyata at pages 3607-08. Additional in vivo functional experimentation with the CR-50 antibody is proposed to further elucidate the role of Reelin in developing brains. *Id.* at page 3609. Unlike de Bergeyck, in which peptides are used to produce and characterize novel antibodies, Miyata is concerned only with using a known antibody.

Miyata does not suggest producing additional antibodies, and there is no apparent advantage to producing an additional monoclonal antibody that recognizes the same epitope as an existing monoclonal antibody. Thus, the reason de Bergeyck provides for producing an isolated epitope peptide is not relevant to the teachings of Miyata, and there is no motivation to combine the references as suggested by the Examiner. The combination of references, therefore, neither suggests nor teaches producing a polynucleotide encoding a polypeptide recognized by a monoclonal antibody to Reelin protein that binds SEQ ID NO:2 and contains neither a repeat site nor an N-terminal region of the Reelin protein that has homology to F-spondin, as recited in the present claims.

Nor does Nakajima cure the defects of de Bergeyck and Miyata. Nakajima discloses the potential role of the CR-50 epitope on Reelin in hippocampus development, based on the ability of CR-50 to disrupt organized development of the hippocampus in vivo. Nakajima at abstract, page 8196. Nakajima also suggests "[f]urther precise mapping and analysis of the CR-50 epitope region . . . to formulate a hypothesis on the mode of interaction between Reelin and other molecules." *Id.* at page 8200. Like Miyata, Nakajima is concerned only with using a known antibody. Nakajima does not propose novel antibodies to Reelin, and there is no apparent advantage to producing an additional monoclonal antibody that recognizes the same epitope as an existing monoclonal antibody. Without a suggestion to generate novel antibodies in Nakajima, there is no motivation to modify the methods of de Bergeyck to isolate a peptide that binds to the CR-50 antibody. Thus, there is no motivation to combine the two references or to produce a polynucleotide encoding a polypeptide that is recognized

by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2, and that contains neither a repeat site nor an N-terminal region of the Reelin protein that has homology to F-spondin, as recited in the present claims.

None of the three references, alone or in combination, teaches or suggests the inventions of claims 4-8, 10, and 11, and there is no teaching, suggestion, or motivation to combine them. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner does not consider the application to be in condition for allowance, Applicants request that the Examiner call the undersigned ((650) 849-6743) to arrange an interview prior to taking action.

Please grant any further extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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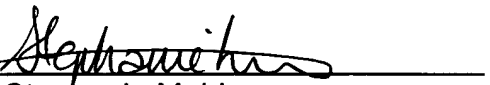
Dated: May 20, 2005

By: 
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